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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/068,751	11/02/98	FRANZ W	690-110PCT

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EXAMINER	
SCHMIDT, M	
ART UNIT	**PAPER NUMBER**
1635	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/068,751	Applicant(s) FRANZ ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- Th MAILING DATE of this communication appears on th cover sheet with the corr spondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-73 and 76-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-73 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Claims 52-73 and 76-79 are currently pending upon entry of both the amendment filed 12/28/00 and the copy of the supplemental amendment originally mailed by Applicant on 5/18/00, but not entered at that time. Upon cancellation of claims 1-51, the 35 U.S.C. 101 and 35 U.S.C. 102 rejections made in the previous Official Action mailed 6/28/00 are removed. The 35 U.S.C. 112, first paragraph, scope of enablement (in view of the claim amendments, the rejection was amended to a scope of enablement rejection), and 35 U.S.C. 103 rejections stand. The rejections as applied to the newly amended claims appear below as well as responses to Applicant's arguments.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The disclosure is objected to because of the following informalities: The brief description of the figures needs to reference the plasmids by SEQ ID NO.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 57, 63, 69 and 70 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 appears to be a Markush claim, but does not correctly claim the groups under a Markush format.

Claim 63 is improperly dependent on claim 62. Claim 62 is drawn to an adenovirus vector. Claim 63 is drawn to an adeno-associated virus vector. It appears claim 63 should depend from claim 61.

Claim 69 is incomplete since there is no final step reading back to the preamble. Specifically, there is no step specifying that the claimed construct is delivered to the muscle cells as stated in the preamble.

Claim 70 lacks antecedent basis for "subject" since no subject is mentioned in claim 69.

5. Claims 69-71 and 76-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific Ad-rsvLuc composition exemplified in the specification as filed administered via direct injection to the cardiac tissue and methods of expression of said construct via direct injection into cardiac tissue and the methods for expression in mice taught by Franz et al. (Cir. Res. 73 (4), p. 629-38), does not reasonably provide enablement for the scope of compositions claimed for expression in any whole organism via any

route of administration as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant's arguments filed 5/18/00 and 12/28/00 have been fully considered but they are not persuasive.

The composition claims 52-68, 74-75 and 78-79 as amended add the limitation "wherein the regulatory nucleic acid sequence is effective for cardiac tissue specific expression of the nucleic acid sequence to be expressed under conditions of somatic gene transfer".

First, on page 5 of the response filed 5/18/00, Applicant argues that Losardo et al. and Rosengart et al. "show that gene therapy has been successfully employed in treatment of myocardial ischemia (angina) by inducing heart muscle localized angiogenesis by over expression of a vascular endothelial growth factor gene. In both instances the promoter used was a CMV promoter, thus constitutive and in this manner distinct from that of the present invention. The vectors employed in these studies were a plasmid DNA (Losordo) and a crippled adenovirus vector (Rosengart). Thus, Rosengart used a vector similar to that described in the present specification as to components other than the expression cassette. Applicants submit that the Losordo and Rosengart papers establish that gene therapy can be accomplished successfully using an adenovirus vector using a route of administration (injection into the heart cavity, see Losordo at p. 280, col. 1, lines 8-14) described in the specification (p. 21, paragraph 8)." In response,

although it was known in the art that certain vectors are effective for gene therapy of a particular genetic target via certain routes of administration, such results do not correlate to gene therapy of any target. As argued previously, however, the field of gene therapy is highly unpredictable. Although Losordo et al. and Rosengart et al. teach the ability to make and use certain gene therapeutic constructs, they do not correlate to the constructs taught in the specification as filed such that one skilled in the art would be able to use them equivalently for expression of any therapeutic gene from the claimed construct.

Claim Rejections - 35 USC § 103

6. Claims 52-68, 72-73 and 76-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz et al., Arnold et al., Knowleton et.al., Shubeita et al., Navankasattusas et al., Thornburn et al., Goswami et al. and Ricigliano et al., in view of Zaia et al. and Posakoff et al.

Claim 52 is drawn to a recombinant virus vector comprising a virus vector and a nucleic acid construct comprising at least one regulatory nucleic acid sequence of the 5' end of a myosin light chain 2 gene that is operatively linked to a nucleic acid sequence to be expressed, wherein the regulatory nucleic acid sequence is effective for cardiac tissue specific expression of the nucleic acid sequence to be expressed under conditions of somatic gene transfer, wherein said recombinant virus vector is optionally complexed with liposomes. The dependent claims add the following limitations: (1) wherein said at least one regulatory nucleic acid sequence comprises

regulatory elements: HF 1a and 1b consisting of nucleotides 2340 to 2361 of SEQ ID NO:1; (2) MLE1 consisting of nucleotides 2229 to 2241 of SEQ ID NOL1; and wherein said recombinant virus vector is optionally complexed with liposomes; (3) wherein said regulatory nucleic acid sequence is obtained from a mammalian genome; (4) wherein said regulatory nucleic acid sequence is obtained from a human or rodent genome; (5) wherein said regulatory nucleic acid sequence is obtained from a rat genome; (6) wherein said regulatory nucleic acid sequence comprises specific positions with respect to the transcription starting point of a myosin light chain 2 gene; (7) wherein said regulatory nucleic acid sequence also comprises an E box element consisting of nucleotides 2328 to 2333 of SEQ ID NO:1 and/or an HF 2 element consisting of nucleotides 2271 to 2289 of SEQ ID NO:1; (8) wherein said regulatory nucleic acid sequence also comprises a CSS sequence element consisting of nucleotides 682 to 724 of SEQ ID NO:1; (9) wherein the construct is a DNA or RNA sequence; (10) wherein said virus vector is an adenovirus vector or an adeno-associated virus vector; (11) wherein said virus vector is a replication deficient adenovirus vector; (12) wherein said replication deficient adeno-associated virus vector consists of two inverted terminal repetition sequences (ITR); (13) wherein the nucleic acid sequence to be expressed encodes a proteinaceous gene product; (14) wherein the proteinaceous gene product is selected from a dystrophin, a beta adrenergic receptor or a nitric oxide synthetase; (15) wherein the nucleic acid sequence to be expressed encodes an antisense nucleic acid or riboyzme; (16) wherein the nucleic acid to be expressed further comprises one or more non-coding sequences and/or a polyadenylation signal sequence; (17) wherein the nucleic

acid to be expressed further comprises one or more non-coding sequences and/or a polyadenylation signal sequence; (18) further comprising a pharmaceutically acceptable carrier; (19) that expresses said nucleic acid to be expressed specifically in the heart or the heart cavity of a subject to which said composition is administered; and (20) that is effective for delivering said nucleic acid construct to heart muscle.

The amendments to the claims which specify functions of the claimed constructs do not further change the structure of the claimed compositions. The 35 U.S.C. 103 rejections made 10/14/99 and maintained 6/28/00 are modified below to further include Posakoff et al.:

Franz et al., Arnold et al., Knowleton et al., Shubeita et al. Navankasattusas et al., Thornburn et al., Goswami et al., Ricigliano et al. and Zaia et al. are relied upon as set forth in the Official Actions mailed 10/14/99 and 6/28/00. Specifically, Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al. and Goswami et al. teach different MLC-2 promoters and reporter constructs.

Posakoff et al. (U.S. Patent 5,858,351) is relied upon to teach other recombinant adeno-associated virus vectors for delivery of DNA molecules to muscle cells. (See the abstract)

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to make a nucleic acid construct comprising an MLC-2 promoter as taught by Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., or Goswami et al. operatively linked to a nucleic acid sequence to be expressed as taught by any of the cited references (including Zaia et al., which teaches expression of antisense and

ribozyme constructs), and further it would have been prima facie obvious at the time the invention was made to construct a recombinant virus vector such as the ones taught by Posakoff et al. comprising said sequences since Posakoff et al. teach design of adenoviral cardiac specific vectors.

One of ordinary skill in the art would have been motivated to make a nucleic acid construct comprising an MLC-2 promoter as taught by Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., or Goswami et al. operatively linked to a nucleic acid sequence to be expressed as taught by any of the cited references, since they all teach the cardiac specific nature of the MLC-2 promoters and expression constructs thereof (see description of what each reference specifically teaches in the Official Action mailed 10/14/99). Further, one of ordinary skill in the art would have been motivated to construct an adenoviral vector comprising said MCL-2 promoters linked to specific expression products since Posakoff et al. teach the motivation for design of such cardiac specific adenoviral expression vectors and the Franz et al. and the others are relied upon to teach the motivation to selectively expression the MLC-2 gene constructs in cardiac specific cells.

One of ordinary skill in the art would have had a reasonable expectation of success to make a nucleic acid construct comprising an MLC-2 promoter since Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., and Goswami et al. all taught such constructs operatively linked to a nucleic acid sequence to be expressed. Further, one of ordinary skill in the art would have had a reasonable expectation of success to make a

recombinant virus vector comprising a virus vector such as the adenoviral vectors taught Posakoff et al. and the MLC-2 constructs taught by any one of Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., and Goswami et al. since vector construction was well known in the art.

7. The prior art is free of the specific Ad-rsvLuc composition taught in the specification as filed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
March 24, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER